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Applicants: Thomas M. Jessell et al.  
Serial No.: 09/654,462 Group Art Unit: 1632  
Filed : September 1, 2000 Examiner: A.M. Falk, Ph.D.  
For : GENETIC DEMONSTRATION OF REQUIREMENT FOR NKX6.1  
AND NKX2.2 IN VENTRAL NEURON GENERATION

Date of Notice  
of Allowance: December 8, 2003 Confirmation No.: 6093

Issue Fee Paid: March 5, 2004

1185 Avenue of the Americas  
New York, New York 10036  
July 16, 2004

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Sir:

**COMMUNICATION AND  
SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**

Applicants paid the issue fee for U.S. Serial No. 09/654,462 on March 5, 2004. In a petition being filed herewith, applicants petition that U.S. Serial No. 09/654,462 be withdrawn from issue under 37 C.F.R. §1.313(c)(2) in consideration of a Request for Continued Examination ("RCE") in compliance with 37 C.F.R. §1.114 filed herewith so that references not previously of record which are submitted with the accompanying Supplemental Information Disclosure Statement may be considered by the Patent Office.

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**Supplemental Information Disclosure Statement**

Applicants are filing this Supplemental Information Disclosure Statement to supplement the Information Disclosure Statement filed on October 23, 2001, and the supplemental Information Disclosure Statement filed on February 13, 2002 in connection with the subject application.

In accordance with their duty of disclosure under 37 C.F.R. §1.56 and pursuant to 37 C.F.R. §1.97(b)(4), applicants direct the Examiner's attention to the references which are listed on the attached Form PTO-1449 (**Exhibit A**):

1. U.S. Serial No. 09/569,259, filed May 11, 2000 on behalf of Thomas M. Jessell et al., including pending claims (**Exhibit 1**);
2. U.S. Serial No. 10/362,437, filed February 20, 2003 on behalf of Thomas M. Jessell et al., including pending claims (**Exhibit 2**);
3. PCT International Application No. PCT/US01/15290, filed May 11, 2001, International Publication No. WO01/84933 A1, published November 15, 2001 (**Exhibit 3**);
4. PCT International Application No. PCT/US01/27256, filed August 31, 2001, International Publication No. WO02/18545 A1, published March 7, 2002 (**Exhibit 4**);

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5. European Patent Application No. 01968382, filed August 31, 2001, European Publication No. EP1315794, published June 4, 2003 on behalf of The Trustees of Columbia University in the City of New York, including Voluntary Amendment filed March 28, 2003 (**Exhibit 5**);
6. Campbell, G. et al., (1999) "Transducing the Dpp Morphogen Gradient in the Wing of Drosophila: Regulation of Dpp Targets by brinker", *Cell* 96: 553-562 (**Exhibit 6**);
7. Chiang, C. et al., (1996) "Cyclopia and Defective Axial Patterning in Mice Lacking Sonic Hedgehog Gene Function", *Nature* 383: 407-413 (**Exhibit 7**);
8. Dasen, J.S. et al., (1999) "Combinatorial Codes in Signaling and Synergy: Lessons From Pituitary Development", *Curr. Opin. Genet. & Dev.* 9: 566-574 (**Exhibit 8**);
9. Ding, Q. et al., (1998) "Diminished Sonic Hedgehog Signaling and Lack of Floor Plate Differentiation in Gli2 Mutant Mice", *Development* 125: 2533-2543 (**Exhibit 9**);
10. Doetsch, F. et al., (1999) "Subventricular Zone Astrocytes Are Neural Stem Cells in the Adult Mammalian Brain", *Cell* 97: 703-716 (**Exhibit 10**);
11. Erskine, L. et al. (1998) "Progenitor Dispersal and the Origin of Early Neuronal Phenotypes in the Chick Embryo Spinal Cord" *Dev. Biol.* 199: 26-41 (**Exhibit 11**);

12. Funayama, N. et al. (1999) "Coelom Formation: Binary Decision of the Lateral Plate Mesoderm is Controlled by the Ectoderm" *Development* 126: 4129-4138 (**Exhibit 12**);
13. Gage, F.H. (2000) "Mammalian Neural Stem Cells", *Science* 287:1433-1438 (**Exhibit 13**);
14. Huang, A.M. et al. (1997) "An Anteroposterior Dorsal Gradient in the Drosophila Embryo", *Genes & Dev.* 11: 1963-1973 (**Exhibit 14**);
15. Ingham, P.W. (1998) "Transducing Hedgehog: The Story So Far" *EMBO J.* 17: 3505-3511 (**Exhibit 15**);
16. Jazwinska, A. et al. (1999) "The Drosophila Gene brinker Reveals a Novel Mechanism of Dpp Target Gene Regulation", *Cell* 96: 563-573 (**Exhibit 16**);
17. Johansson, C.B. et al. (1999) "Identification of a Neural Stem Cell in the Adult Mammalian Central Nervous System", *Cell* 96: 25-34 (**Exhibit 17**);
18. Kraut, R. et al. (1991) "Spatial Regulation of the Gap Gene giant During Drosophila Development", *Development* 111: 601-609 (**Exhibit 18**);
19. Krishnan, V. et al. (1997) "Mediation of Sonic Hedgehog-Induced Expression of COUP-TFII by a Protein Phosphatase", *Science* 278: 1947-1950 (**Exhibit 19**);

20. Lawrence, P.A. et al. (1996) "Morphogens, Compartments, and Pattern: Lessons from Drosophila?", *Cell* 85: 951-961 (**Exhibit 20**);
21. Lewis, K.E. et al. (1999) "Expression of *ptc* and *gli* Genes in *talpid*<sup>3</sup> Suggests Bifurcation in Shh Pathway" *Development* 126: 2397-2407 (**Exhibit 21**);
22. Mansouri, A. et al. (1998) "Pax3 and Pax7 are Expressed in Commissural Neurons and Restrict Ventral Neuronal Identity in the Spinal Cord", *Mech. Dev.* 78: 171-178 (**Exhibit 22**);
23. Marti, E. et al. (1995) "Distribution of Sonic Hedgehog Peptides in the Developing Chick and Mouse Embryo", *Development* 121: 2537-2547 (**Exhibit 23**);
24. Matisse, M.P. et al. (1998) "Gli2 is Required for Induction of Floor Plate and Adjacent Cells, But Not Most Ventral Neurons in the Mouse Central Nervous System", *Development* 125: 2759-2770 (**Exhibit 24**);
25. McDowell, N. et al. (1999) "Activin as a Morphogen in *Xenopus* Mesoderm Induction", *Semin. Cell & Dev. Biol.* 10: 311-317 (**Exhibit 25**);
26. Minami, M. et al. (1999) "Brinker is a Target of Dpp in *Drosophila* that Negatively Regulates Dpp-dependent Genes", *Nature* 398: 242-246 (**Exhibit 26**);

27. Papin, C. et al. (2000) "Gradual Refinement of Activin-Induced Thresholds Requires Protein Synthesis" *Dev. Biol.* 217: 166-172 (**Exhibit 27**);
28. Pierani, A. et al. (1999) "A Sonic Hedgehog-Independent, Retinoid-Activated Pathway of Neurogenesis in the Ventral Spinal Cord", *Cell* 97: 903-915 (**Exhibit 28**);
29. Roelink, H. et al. (1995) "Floor Plate and Motor Neuron Induction by Different Concentrations of the Amino-Terminal Cleavage Product of Sonic Hedgehog Autoproteolysis", *Cell* 81: 445-455 (**Exhibit 29**);
30. Rowitch, D.H. et al. (1999) "Sonic hedgehog Regulates Proliferation and Inhibits Differentiation of CNS Precursor Cells", *J. Neurosci.* 19: 8954-8965 (**Exhibit 30**);
31. Ruiz i Altaba, A. (1999) "Gli. Proteins and Hedgehog Signaling: Development and Cancer", *Trends Genet.* 15: 418-425 (**Exhibit 31**);
32. Sharma, K. et al. (1998) "LIM Homeodomain Factors Lhx3 and Lhx4 Assign Subtype Identities for Motor Neurons", *Cell* 95: 817-828 (**Exhibit 32**);
33. Smith, J.C. (1995) "Mesoderm-Inducing Factors and Mesodermal Patterning", *Curr. Opin. Cell Biol.* 7: 856-861 (**Exhibit 33**);

34. Tanabe, Y. et al. (1998) "Specification of Motor Neuron Identity by the MNR2 Homeodomain Protein", *Cell* 95: 67-80 (**Exhibit 34**);
  35. Wu, X. et al. (1998) "Two Distinct Mechanisms for Differential Positioning of Gene Expression Borders Involving the Drosophila Gap Protein Giant", *Development* 125: 3765-3774 (**Exhibit 35**);
  36. Horner et al. (2000) "Regenerating the Damaged Central Nervous System", 407: 963-970;
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  39. Langman, J. et al. (1966) "Behavior of Neuroepithelial Cells During Closure Of The Neural Tube", *J. Comp. Neur.* 127: 399-411;
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42. Sander, M. et al. (2000) "Ventral Neural Patterning By Nkx Homeobox Genes: Nkx6.1 Controls Somatic Motor Neuron And Ventral Interneuron Fates", *Genes & Development* 14(17): 2134-2139;
43. Struhl, G. et al. (1992) "Control Of Drosophila Body Pattern By The hunchback Morphogen Gradient", *Cell* 69: 237-249;
44. Yamada, T. et al. (1993) "Control Of Cell Pattern In The Neural Tube: Motor-Neuron Induction By Diffusible Factors From Notochord And Floor Plate", *Cell* 73: 673-686;
45. Basler, K. et al. (1993) "Control of cell pattern in the neural tube: Regulation of cell differentiation by dorsalin-1, a novel TGF $\beta$  family member", *Cell* 73: 687-702 (**Exhibit 36**);
46. Briscoe, J., and Ericson, J. (2001) "Specification of neuronal fates in the ventral neural tube", *Curr. Opin. Neurobiol.* 11: 43-49 (**Exhibit 37**);
47. Briscoe, J. et al. (2001) "A hedgehog-insensitive form of patched provides evidence for direct long-range patterning activity of Sonic hedgehog in the neural tube", *Molecular Cell* 7: 1279-1291 (**Exhibit 38**);
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chicken Nkx-6.2 homeobox gene suggest its possible involvement in the ventral neural patterning and cell fate specification", *Dev. Dyn.* 216: 459-468 (**Exhibit 39**);

49. Davis, C.A. et al. (1991) "Examining pattern formation in mouse, chicken and frog embryos with an En-specific antiserum", *Development* 111: 287-298 (**Exhibit 40**);

50. Eberhard, D. et al. (2000) "Transcriptional repression by Pax5 (BSAP) through interaction with corepressors of the Groucho family" *EMBO J.* 19: 2292-2303 (**Exhibit 41**);

~~51. Hoshiyama, D. et al. (1998) "Sponge Pax cDNA related to Pax-2/5/8 and ancient gene duplications in the Pax family", *J. Mol. Evol.* 47: 640-648 (**Exhibit 42**);~~

52. Jørgensen, M.C. et al. (1999) "Cloning and DNA-binding properties of the rat pancreatic beta-cell-specific factor Nkx6.1", *FEBS Lett.* 461: 287-294 (**Exhibit 43**);

53. Kraut, R. and Levine, M. (1991) "Mutually repressive interactions between the gap genes giant and Kruppel define middle body regions of the *Drosophila* embryo" *Development* 111: 611-621 (**Exhibit 44**);

54. Komuro, I. et al. (1993) "Gtx: a novel murine homeobox-containing gene, expressed specifically in glial cells of the brain and germ cells of testis, has a transcriptional repressor activity in vitro for a serum-inducible promoter" *EMBO* 12: 1387-1401 (**Exhibit 45**);

55. Lee, S. et al. (2001) "Cloning, expression and chromosomal location of NKX6B to 10q26, a region frequently deleted in brain tumors", *Mammalian Genome* 12: 157-162 (**Exhibit 46**);
56. Mombaerts, P. et al. (1996) "Visualizing an olfactory sensory map", *Cell* 87: 675-686 (**Exhibit 47**);
57. Moran-Rivard, L. et al. (2001) "Evx1 is a postmitotic determinant of V0 interneuron identity in the spinal cord", *Neuron* 29: 385-399 (**Exhibit 48**);
58. Muhr, J. et al. (2001) "Groucho-mediated transcriptional repression establishes progenitor cell pattern and neuronal fate in the ventral neural tube", *Cell* 104: 861-873 (**Exhibit 49**);
59. Novitsch, B. et al. (2001) "Coordinate regulation of motor neuron subtype identity and pan-neural properties by the bHLH repressor Olig2", *Neuron* 31: 773-789 (**Exhibit 50**);
60. Nutt, S.L. et al. (1999) "Commitment to the B-lymphoid lineage depends on the transcription factor Pax5", *Nature* 401: 556-562 (**Exhibit 51**);
61. Pabst, O. et al. (2000) "NKX2 gene expression in neuroectoderm but not in mesendodermally derived structures depends on sonic hedgehog in mouse embryos", *Dev. Genes. Evol.* 210: 47-50 (**Exhibit 52**);

62. Peters, T. et al. (2000) "Organization of mouse Iroquois homeobox genes in two clusters suggests a conserved regulation and function in vertebrate development", *Genome Res.* 10: 1453-62 (**Exhibit 53**);
63. Pierani, A. et al. (2001) "Control of interneuron fate in the developing spinal cord by the progenitor homeodomain protein Dbx1" *Neuron* 29: 367-384 (**Exhibit 54**);
64. Rolink, A.G. et al. (1999) "Long-term in vivo reconstitution of T-cell development by Pax5-deficient B-cell progenitors", *Nature* 401: 603-606 (**Exhibit 55**);
65. Schäeren-Wiemers, N. and Gerfin-Moser, A. (1993) "A single protocol to detect transcripts of various types and expression levels in neural tissue and cultured cells: in situ hybridization using digoxigenin-labeled cRNA probes", *Histochemistry* 100: 431-440 (**Exhibit 56**);
66. Shoji, H. et al. (1996) "Regionalized expression of the Dbx family homeobox genes in the embryonic CNS of the mouse", *Mech. Dev.* 56: 25-39 (**Exhibit 57**);
67. Stanojevic, D., Small, S. and Levine, M. (1991) "Regulation of a segmentation stripe by overlapping activators and repressors in the *Drosophila* embryo", *Science* 254: 1385-1387 (**Exhibit 58**);
68. Tanaka, M., Yamasaki, N., Izumo, S. (2000) "Phenotypic

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characterization of the murine Nkx2.6 homeobox gene by gene targeting", *Mol. Cell. Biol.* 20: 2874-2879 (**Exhibit 59**);

69. Toresson, H., Potter, S.S. and Campbell, K. (2000) "Genetic control of dorsal-ventral identity in the telencephalon: opposing roles for Pax6 and Gsh2", *Development* 127: 4361-4371 (**Exhibit 60**);
70. Wang, C.C. et al. (2000) "Conserved linkage of NK-2 homeobox gene pairs Nkx2-2/2-4 and NK-2-1/2-9 in mammals", *Mamm. Genome* 11: 466-468 (**Exhibit 61**);
71. Yun, K., Potter, S. and Rubenstein, J.L. (2001) "Gsh2 and Pax6 play complementary roles in dorsoventral patterning of the mammalian telencephalon", *Development* 128: 193-205 (**Exhibit 62**); and
72. Canadian Patent Application No. 2,419,851, filed August 31, 2001, on behalf of The Trustees of Columbia University in the City of New York, including a copy of August 25, 2003 Voluntary Amendment (**Exhibit 63**).

The subject application is a continuation-in-part and claims the benefit under 35 U.S.C. §120 of U.S. Serial No. 09/569,259, filed May 11, 2000, a copy of which is attached hereto as **Exhibit 1**. Above listed references 38-44 were submitted to and considered by the United States Patent and Trademark Office in a supplemental Information Disclosure Statement filed on January 28, 2002 in connection with U.S.

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Serial No. 09/569,259, filed May 11, 2000. Above listed references 36 and 37 were cited by the United States Patent and Trademark Office in an Office Action dated August 1, 2002 in connection with U.S. Serial No. 09/569,259, filed May 11, 2000. Accordingly, under 37 C.F.R. §1.98(d) copies of these references are not required to be provided to the United States Patent and Trademark Office, since they were previously submitted to and considered by the United States Patent and Trademark Office.

U.S. Serial No. 10/362,437, filed February 20, 2003 claims the benefit under 35 U.S.C. §120 of PCT International Application No. PCT/US01/27256, filed August 31, 2001, which claims priority of and benefit under 35 U.S.C. §120 of the subject application. A copy of which is attached hereto as **Exhibit 2**.

PCT International Application No. PCT/US01/15290, filed May 11, 2001, is a foreign counterpart application and claims priority of U.S. Serial No. 09/569,259, filed May 11, 2000, of which the subject application is a continuation-in-part and claims priority. A copy of which international application is attached hereto as **Exhibit 3**. A Search Report was issued on August 29, 2001 in connection with PCT International Application No. PCT/US01/15290, filed May 11, 2001. A copy of the Search Report is attached hereto as **Exhibit B**. Above listed reference 30 was cited in the Search Report, a copy of which is attached hereto as **Exhibit 30**. The remaining references cited in the Search Report were previously submitted to and considered by the United States Patent and Trademark Office in an Information Disclosure Statement filed

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on October 23, 2001 in connection with the subject application.

PCT International Application No. PCT/US01/27256, filed August 31, 2001, is a continuation-in-part and claims priority of the subject application. A copy of which is attached hereto as **Exhibit 4**.

European Patent Application No. 01968382, filed August 31, 2001, European Publication No. EP1315794, published June 4, 2003, claims priority of PCT International Application No. PCT/US01/27256, filed August 31, 2001, which claims priority of and benefit under 35 U.S.C. §120 of the subject application. A copy of which is attached hereto as **Exhibit 5**.

Canadian Patent Application No. 2,419,851, filed August 31, 2001 claims priority of PCT International Application No. PCT/US01/27256, filed August 31, 2001, which claims priority of and benefit under 35 U.S.C. §120 of the subject application. A copy of which is attached hereto as **Exhibit 63**.

References 6-35 and 45-71 are attached hereto as Exhibits 6-62, respectively.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

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No fee, other than the \$385.00 RCE filing fee, included in the enclosed check for \$515.00, is deemed necessary in connection with the filing of this Communication and supplemental Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "John P. White", is written over a horizontal line.

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Registration No. 28,678  
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<b>Form PTO-1449</b>		<b>U.S. Department of Commerce Patent and Trademark Office</b>		Atty. Docket No. <b>0575/62166/JPW/MVM</b>		Serial No. <b>09/654,462</b>						
<b>INFORMATION DISCLOSURE STATEMENT</b> (Use several sheets if necessary)				Applicants <b>Thomas M. Jessell et al.</b>								
				Filing Date <b>September 1, 2000</b>		Group <b>1632</b>						
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	WO	0	1	8	4	9	3	3	11/15/01	PCT (Exhibit 3);		
	WO	0	2	1	8	5	4	5	03/07/02	PCT (Exhibit 4);		
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>												
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**Exhibit A**



<b>Form PTO-1449</b>		<b>U.S. Department of Commerce Patent and Trademark Office</b>			Atty. Docket No. 0575/62166/JPW/MVM		Serial No. 09/654,462	
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	Doetsch, F. et al., (1999) "Subventricular Zone Astrocytes Are Neural Stem Cells in the Adult Mammalian Brain", <i>Cell</i> 97: 703-716 ( <b>Exhibit 10</b> );							
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